

where  $s^\circ$  and  $D^\circ$  are the sedimentation and translational diffusion coefficients at infinite dilutions,  $\nu$  is the partial specific volume of the micelle,  $T$  is the temperature,  $R$  is the universal gas constant, and  $\rho$  is the solvent density.

In order to obtain  $s^\circ$  and  $D^\circ$  experimentally, both sedimentation coefficients and translational diffusion coefficients of the micellar solutions need to be measured. Sedimentation coefficients of the micellar solutions can be measured either by scanning using an analytical ultracentrifuge such as Beckman E equipped with a photoelectrical scanning device with monochromator and multiplexor or using a schlieren mode available on the same equipment with a schlieren-optic registration system. The (z-average) translational diffusion coefficients can be determined by quasielastic light-scattering method using an Autosizer 2c (Malvern) small-angle laser photometer. The  $s^\circ$  and  $D^\circ$  values are then determined using the extrapolation of the sedimentation and translational diffusion coefficients to infinite dilutions. The  $\nu$  value can be determined using a pycnometer. Dynamic light-scattering measurements for estimation of unimer diffusion coefficients can be made using the Brookhaven Model BI-200SM laser light-scattering system (Brookhaven Instrument Corporation) at a scattering angle of  $90^\circ$  (Goldmints et al., 1997).

### Micelle Size and Size Distribution

Small size (10–100 nm) is one of the most interesting features of polymeric micelles. Besides allowing the extravasation of the carriers, it permits the sterilization of the preparation to be done simply by filtration and minimizes the risks of embolism in capillaries, contrary to larger drug carriers (Kwon and Okano, 1996). Micellar size seldom exceeds 100 nm, but depends on several factors, including copolymer molecular weight, relative proportion of hydrophilic and hydrophobic chains, and aggregation number (Yokoyama et al., 1990; Trubetskoy and Torchilin, 1996; Shin et al., 1998).

Micellar diameter and size polydispersity can be obtained directly in water or in an isotonic buffer by DLS. DLS can also provide some information on the sphericity of polymeric micelles (Kataoka et al., 1996; Nagasaki et al., 1998). Ultracentrifugation velocity studies are sometimes performed to assess the polydispersity of polymeric micelles (Yokoyama et al., 1994; Hagan et al., 1996).

Microscopic methods such as atomic force microscopy (AFM) (Cammass et al., 1997; Kohori et al., 1998), transmission electron microscopy (TEM) (Yu et al., 1998), and scanning electron microscopy (SEM) (Kim et al., 1998) have been applied. These methods allow the characterization of the micelle shape and size dispersity. Conventional SEM is widely used in the field of colloidal carriers since it has high resolution and the sample preparation is relatively easy. However, it is analyzed, the samples must withstand high vacuum. Furthermore, the visualization of the particles requires them to be conductive, which is achieved by coating their surface with gold. The thickness of the coating, which can reach several nanometers, has to be taken into account in the size determination. New imaging tools such as AFM enable the visualization of polymeric micelles at atmospheric pressure without gold coating (Allemann et al., 1998). By AFM, Cammass et al. (1997) showed that micelles of poly(*N*-isopropylamide)-block-polystyrene (PNIPA-*b*-PST) had a discus shape with a 5 nm height and a 20 nm diameter, which was close to the 24 nm size measured by DLS.

Size measurements can be done to study the interaction of polymeric micelles with biological media (Jones and Leroux, 1999). For instance, PEO-*b*-PPO-*b*-PEO micelles were found to maintain their initial size in the presence of antibodies and bovine serum albumin, suggesting the apparent absence of interaction with plasma proteins (Kabanov et al., 1992).

### Lower Critical Solution Temperature and Cloud Point

As is being discussed, polymers used to prepare micelles exhibit a LCST that can be defined as the temperature at which the polymer phase separates (Heskins and Guillet, 1968). Below the LCST, the polymer/micelle is soluble, but it precipitates at temperatures above the LCST. The diameter of these micelles rapidly rises at temperatures above the LCST, due to hydrophobic interactions that result in the aggregation of the micelles (Kohori et al., 1998). This effect of temperature on size was